SYNTHESIS OF MACROLIDE ANTIBIOTICS

COMMUNICATION 2.* SYNTHESIS OF THE C^9-C^{13} FRAGMENT OF ERYTHRONOLIDES A AND C AND MEGALONOLIDE

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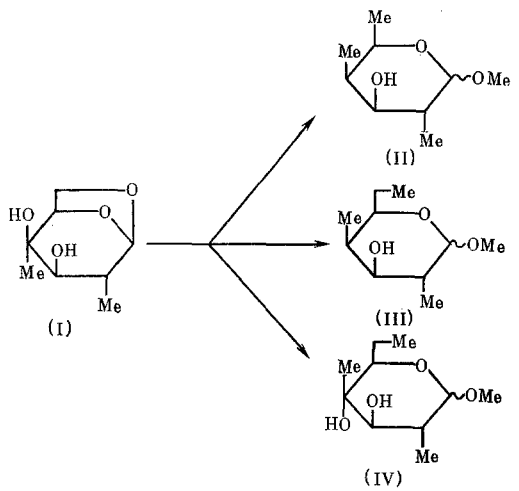
In the preceding paper, we reported the synthesis of the C^1-C^6 fragment of a group of structurally related 14-membered macrolide antibiotics. We here present the results of a search for synthetic routes to the C^9-C^{13} fragments, and report the synthesis of one of these. The key intermediate in the synthesis of compounds of this group, as previously [2], was 1,6-anhydro-2-desoxy-2,4-di-C-methyl-β-D-galactopyranose (I), which can be obtained from levoglucosan in 9 stages in an overall yield of 35% [1, 2].

In order to convert (I) into the C^9-C^{13} fragments of the above-mentioned antibiotics, it is necessary to increase the chain length at C^6 by one carbon atom in the case of the erythromycins, and in the case of oleandomycin, to reduce the primary alcohol group to methyl. For erythromycin B and oleandomycin, it is necessary to carry out deoxygenation at C^4 in (I) and to change the stereochemistry of the methyl group, and for erythromycin this center must be isomerized. The stereochemistry of the other centers of (I) correspond completely with the stereochemistry of the C^9-C^{13} fragments of these antibiotics



Monobenzylation of (I) (CH_3SOCH_2Na/DMSO/BnCl) afforded the 3-O-benzyl ether (V) in high yield, containing only small amounts (5-10%) of the 4-O-benzyl ether. The compound (V) was separated by crystallization, and the residue was further benzylated (NaH/DMF/BnCl) to the dibenzyl ether, which was employed in the synthesis of the C^1-C^6 fragment of the 14-membered macrolide antibiotics, as described in the previous communication [2].

The structures of (V) and the 4-O-benzyl ether follow from a comparison of their ^{13}C NMR spectra with that of (I). In (V), the high-field shift of the signals for C^2 and C^4 and the low-field shift of the C^3 signal indicate alkylation of the HO group at C^3. In the spectrum of the isomeric compound, the slight shift of the C^4 signal as compared with (I) is typical of the alkylation of a tertiary hydroxyl group. Alkylation of the C^4 hydroxyl is also

*For previous communications, see [1, 2].

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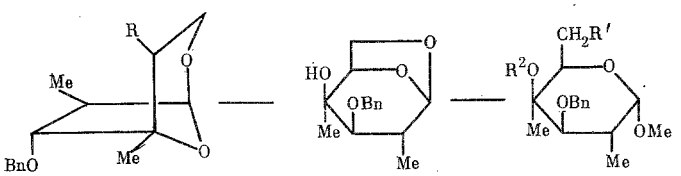
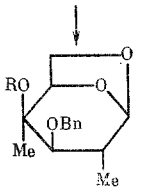
indicated by the high-field shift of the Me group at C^4 and the methylene carbon of the benzyl group. The shift of the latter ($\delta \sim 64$ ppm) is also typical of related systems studied in this laboratory, and provides evidence of the considerable steric hindrance experienced by the methylene group in this position.

Attempts to open the 1,6-anhydro ring in (V) by methanolysis (3% HCl/MeOH at the boil) gave unsatisfactory results. There was isolated from the reaction mixture, in addition to small amounts of the α-methylglycoside (VII), a compound which from its spectra and chemical properties (oxidation to a ketone and formation of a formate on treatment with DMF/MsCl [3]) was assigned the structure 1,6-anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-α-D-galactopyranose (VI).



(VIa-c) (V) (VII) - (XII)



(XIII) - (XIV)

R = OH (VI a); R = OCHO (VIb); R = O (VIc); R′ = OH, R^2 = H (VII); R′ = OMs, R^2 = H (VIII); $R^1 = R^2$ = H (IX); R′ = Me, R^2 = H (X); R′ = H, R^2 = Ms (XI); R′ = Me, R^2 = Ms (XII); R = Ac (XIII); R = Ms (XIV)

Lowering the reaction temperature and increasing the concentration of acid enabled the methanolysis of (V) to be effected (20% HCl/MeOH, 0°C, 48 h) to give high yields of a 9:2 mixture of the α- and β-methylglycosides.

Mesylation of (VII) [MsCl − $(C_2H_5)_3N/CH_2Cl_2$, 10°C] gave the mesylate (VIII), which was reduced in quantitative yield by $LiAlH_4$ to the galactopyranoside (IX). The high rate of the reduction indicated that this was an intramolecular reaction proceeding through the alkoxyaluminohydride (cf. [5]).

Treatment of (VIII) with Me_2CuLi gave high yields of methyl-2,6-didesoxy-2,4,6-tri-C-methyl-3-O-benzyl-α-D-galactopyranoside (X), the formation of which apparently occurred via the tert-alkoxymethylcuprate (cf. [6]). The structures of (IX) and (X) were confirmed by their PMR and ^{13}C NMR spectra.

Compound (IX) differs from the structure of the C^9-C^{13} fragment of oleandonolide in possessing an HO group, and in the stereochemistry at C^4. Similarly, (X) differs from the C^9-C^{13} fragment of erythronolide A in the stereochemistry at C^4, and from the C^9-C^{13} fragment of erythronolide B in the presence of an HO group and the stereochemistry at C^4. In order to convert (IX) and (X) into the corresponding fragments, a study was carried out of the deoxygenation of the corresponding mesylates (XI) and (XII).

When attempts were made to deoxygenate (XI) and (XII) by treatment with lithium trimethoxyaluminohydride−CuI [7] or with lithium triethylborohydride [8], only demesylation occurred, with the formation of the original alcohols (IX) and (X).

Reaction of the mesylate of (X) with tetrabutylammonium formate in acetone or DMF [9], with the aim of inverting the configuration at C^4, was likewise unsuccessful. No reaction occurred in acetone, and demesylation occurred in DMF.

Attempts to obtain the corresponding halides from (IX) and (X) with retention ($PCl_5/CaCO_3$/chloroform, 0°C [10]) or inversion (PH_3PBr_2/CCl_4/HCl/pentane, [11] or Me_3SiBr [12]) of the configuration at C^4 were likewise not crowned with success.

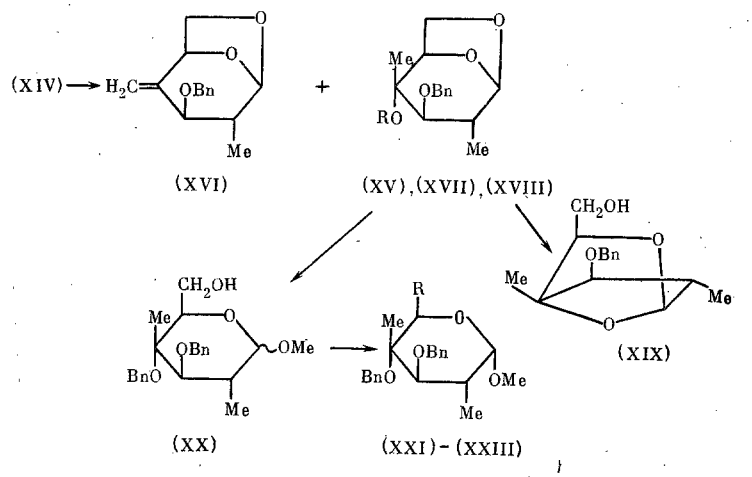
Following these unsuccessful attempts to convert (IX) and (X) into the C^9-C^{13} fragments of the antibiotics, we turned our attention to the bicyclic compounds (XIII) and (XIV), which contain the 1,6-anhydro ring. The following is a brief description of our attempts to deoxygenate or isomerize (XIII) and (XIV).

Reaction of (XIV) with lithium triethylborohydride [8] (at the boil in THF, 8 h) resulted in recovery of the starting material; the use of superhigh pressures in this reaction resulted only in the partial demesylation of (XIV). Electrochemical reduction of (XIV) [13] failed to occur up to the discharge potential of the tetrabutylammonium cation ($\varepsilon > -3.1$ V). Attempts to reduce (XIV) by the method described in [14], as recommended by Brown for tertiary halides, was also unsuccessful.

When deoxygenation was carried out by the modified Birch reaction [15] on the acetate (XIII), only rapid debenzylation occurred (cf. [16]) to give (I) in good yield. A similar result was obtained when attempts were made to carry out the photochemical deoxygenation of the acetate (XIII) in aqueous Hexametapol [17]. When attempts were made to obtain the corresponding halides, the tertiary alcohol (V) either remained unchanged, or rapid destruction of the compound occurred. Ionic hydrogenation was also unsuccessful in this case, as a result of the rapid decomposition of (V) [18].

Further studies were made of the possibility of epimerization at C^4 without deoxygenation to obtain the C^9-C^{13} fragment of erythronolide A (IV). When (XIV) was boiled in nitromethane, a mixture of products was obtained, from which the isomeric mesylate (XV) was isolated in 30% yield. Isomerization was accompanied by partial cleavage of methanesulfonic acid, the presence of which in the reaction mixture resulted in rapid decomposition. When the reaction was carried out in the presence of 4 Å molecular sieves, which bind MsOH, no resinification occurred, and the yield of (XV) rose to 59%. Another reaction product was the methylene derivative (XVI), the structure of which followed from a comparison of its PMR and ^{13}C NMR spectra with those of its 3-O-methyl analog [19]. This compound was used subsequently for the synthesis of the C^9-C^{13} fragments of erythronolide B and oleandonolide (see the following communication).

Thus, after many attempts, conditions were found for the preparation of (XV) in which the configurations of all the chiral centers corresponded to the C^9-C^{13} fragment of erythronolide A. In order to convert (XV) into the same fragment, it is necessary to increase the chain length at C^6 by one carbon atom.



R = Ms (XV); R = H (XVII); R = Bn (XVIII); R = CHO (XXI); R = CH_2 = CH (XXII); R = C_2H_5 (XXIII).

Demesylation of (XV) with $LiAlH_4$ gave qualitative yields of the alcohol (XVII), which, like the isomeric compound (V), was subjected to methanolysis (20% HCl/MeOH, 0°C). However, despite the fact that the expected mixture of anomeric methylglycosides was qualitatively observed at the intermediate stages, the overall reaction resulted in the formation of 1,4-anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-α-D-glycopyranose (XIX), the structure of which followed from a study of its spectra (cf. Experimental). An attempt to first protect the C^4 hydroxyl group as its allyl ether did not improve the outcome. Methanolysis was successful only after conversion of the tertiary OH group in (XVII) into the O-benzyl ether (XVIII). When the methanolysis of the latter was effected under our conditions, a mixture of anomeric methylglycosides (XX) was obtained.

The methylglycosides (XX) were oxidized to an anomeric mixture of aldehydes (XXI), and the α-anomer of (XXI), isolated by chromatography, was subjected to the Wittig reaction. The resulting vinyl derivative (XXII), following reduction with $LiAlH_4-CoCl_2$ [20], gave good yields of methyl 2,6-desoxy-2,4,6-tri-C-methyl-3,4-di-O-benzyl-α-D-glycopyranoside (XXIII), which is the C^9-C^{13} fragment of erythronolide A, the OH groups of which were protected by groups convenient for the later reactions. The structures of (XXIII) and the other intermediates followed from their PMR and ^{13}C NMR spectra.

EXPERIMENTAL

PMR spectra were obtained on Tesla BS-497 and Bruker WM-250 instruments, and ^{13}C NMR spectra on Bruker WP-60 and Bruker WM-250 instruments ($CDCl_3$ solutions, internal standard TMS, $\delta = 0$, J in Hz). Specific rotations were measured on a Perkin–Elmer M-141 polarimeter, in chloroform. The course of the reactions and the purity of the products were followed by TLC on silica gel L (5-40 mμ), and by GLC on an LKhM-8MD (column with 3% SE-30 on Chromaton NAW-DMCS, length 2 m) or a Biochrom-21 instrument (glass capillary column, OV-101, length 50 m). Mixtures were separated by column chromatography on Silpearl silica gel (25-40 mμ), using continuous linear solvent gradients and an overpressure of 0.5-1.2 atm.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-β-D-galactopyranose (V) and 1,6-Anhydro-2-desoxy-2,4-di-C-methyl-4-O-benzyl-β-D-galactopyranose. To a solution of 9.3 g (53.5 mmole) of (I) in 60 ml of dry DMSO was added 43.6 ml of a 1.286 N solution of CH_3SOCH_2Na (56.1 mmole). After 20 min, 6.98 g (55.1 mmole) of $PhCh_2Cl$ was added, and after 1 h the mixture was poured into 1 l of water, and extracted with chloroform (3 × 100 ml). The organic layer was washed with saturated NaCl solution, dried, and evaporated in vacuo. The residue was recrystallized from ether–hexane (1 : 5) to give 8.9 g (63%) of (V), mp 57.5-58°C, $[\alpha]_D^{22}$ −89°C (c, 1.0). PMR spectrum (δ, ppm): 5.24 d 1H, $J_{1,2}$ = 1 Hz, H^1), 2.24 d.d (1H, J_{2,CH_3} = 8 Hz, H^2), 3.14 s (1H, H^3), 3.87 s (1H, OH), 4.02 d.d (1H, $J_{5,6\ endo}$ = 1 Hz, $J_{5,6\ exo}$ = 6 Hz, H^5), 4.25 d (1H, $J_{6,6'}$ = 7.5 Hz, $H^{6\ endo}$), 3.62 d.d (1 H, $H^{6\ exo}$), 4.54 AB (2H, CH_2Ph), 7.30 s (5H, C_6H_5), 1.44 s (3H, CH_3 at C^4), 1.07 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 103.1 (C^1), 38.2 (C^2), 83.8 (C^3), 67.9 (C^4), 79.1 (C^5), 63.7 (C^6), 72.1 (CH_2Ph at C^3), 26.6 (CH_3 at C^4), 16.4 (CH_3 at C^2). Found: C 67.91; H 7.59%. $C_{15}H_{20}O_4$. Calculated: C 68.18; H 7.50%.

The mother liquors from the crystallization were chromatographed to give a further 2.82 g (20%) of (V) and 1.68 g (12%) of the 4-O-benzyl ether, syrup, $[\alpha]_D^{22}$ −18.3° (c, 1.0). PMR spectrum (δ, ppm): 5.26 d (1H, $J_{1,2}$ = 1 Hz, H^1), 2.18 d.q (1H, J_{2,CH_3} = 7.5 Hz, H^2), 3.54 s (1H, H^3), 4.21 d.d (1H, $J_{5,6\ endo}$ = 1 Hz; $J_{5,6\ exo}$ = 5.5 Hz, H^5), 4.42 d.d (1H, $J_{6,6'}$ = 7.5 Hz, $H^{6\ endo}$), 3.60 d.d (1H, $H^{6\ exo}$), 4.55 AB (2H, CH_2Ph), 7.35 s (5H, C_6H_5), 3.12 s (1H, OH), 1.44 s (3H, CH_3 at C^4), 1.09 d (3H, J_{2,CH_3} = 8 Hz, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.7 (C^1), 42.1 (C^2), 75.4 (C^3), 73.4 (C^4), 77.2 (C^5), 64.0 (C^6), 64.2 (CH_2Ph at C^4), 22.5 (CH_3 at C^4), 16.0 (CH_3 at C^2), 137.4 128.6, 137.9, 127.6 (C_6H_5).

Methyl 2-Desoxy-2,4-di-C-methyl-3-O-benzyl-α-D-galactopyranoside (VII). a) A solution of 9.80 g (37.1 mmole) of (V) in 100 ml of 3% HCl in MeOH was boiled for 3 h, neutralized with IRA-400 (CO_3^{2-}), the resin filtered off, and the filtrate evaporated. The residue was chromatographed to give 1.89 g (17.2%) of (VII) and 2.21 g (21.7%)of (VIa), syrup, $[\alpha]_D^{22}$ +36.0° (c, 1.0).

b) To a solution of 5 g of HCl in 18 ml of MeOH was added 2 g (7.6 mmole) of (V), and the mixture was kept at −5°C until the starting material was no longer present (~ 60 h). The mixture was diluted with 100 ml of dry ether, and neutralized with gaseous NH_3, with cooling. The NH_4Cl was filtered off and washed with ether, and the filtrate was evaporated. Chromatography of the residue gave 1.564 g (70 %) of (VII), syrup, $[\alpha]_D^{21}$ +109° (c, 1.0). PMR spectrum (δ, ppm): 5.10 d (1H, $J_{1,2}$ = 5 Hz, H^1), 2.39 m (1H, H^2), 3.75 d (1H, $J_{2,3}$ = 4.5 Hz, H^3), 3.2 d.d (1H, $J_{5,6}$ = $J_{5,6'}$ = 10.5 Hz, H^5), 3.75 d.d (1H, $J_{6,6'}$ = 6.5 Hz, H^6), 3.8 d.d (1H, H^6), 4.57 s (2H, CH_2Ph), 7.34 s (5H, C_6H_5), 3.62 s (1H, OH), 1.42 s (3H, CH_3 at C^4), 1.16 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 99.7 (C^1), 47.3 (C^2), 82.7 (C^3), 85.7 (C^4), 67.8 (C^5), 63.9 (C^6), 71.6 (CH_2Ph), 138.3 :128.0 :127.1 (C_6H_5), 17.0 (CH_3 at C^4), 10.8 (CH_3 at C^2).

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-5-O-formyl-L-D-galactofuranose (VIb). To a solution of 0.17 g (0.64 mmole) of (VI) in 1.7 ml of dry DMF was added 1 ml of MsCl, and the mixture was heated for 2 h at 65°C. The mixture was then evaporated, and the residue chromatographed to give 0.105 g (56%) of a syrup. PMR spectrum (δ, ppm): 5.05 d (1H, $J_{1,2}$ = 4.7 Hz, H^1), 2.2 m (1H, H^2), 3.65 d (1H, $J_{2,3}$ = 4.5 Hz, H^3), 4.90 d.d (1H, $J_{5,6\ endo}$ = 10 Hz; $J_{5,6\ exo}$ = 6.5 Hz, H^5), 3.95 d.d (1H, $J_{6,6'}$ = 11 Hz, $H^{6\ exo}$), 3.16 d.d (1H, $H^{6\ endo}$), 4.48 s (2H, CH_2Ph), 7.92 s (1H, CHO), 1.08 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2), 1.28 s (3H, CH_3 at C^4).

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-α-L-arabinohexuloso-5-furanose (VIc). Oxidation of (VI) with $(COCl)_2$–DMSO [2] afforded (VIc) as a syrup, yield 98%. PMR spectrum (δ, ppm): 5.33 d (1H, $J_{1,2}$ = 4.5 Hz, H^1), 2.33 m (1H, H^2), 3.3 d (1H, $J_{3,4}$ = 4 Hz, H^3), 4.13 d.d (2H, H^6, $H^{6'}$), 4.5 s (2H, CH_2Ph), 7.3 s (5H, C_6H_5), 1.42 s (3H, CH_3 at C^4), 1.1 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 99.9 (C^1), 48.0 (C^2), 86.0 (C^3), 90.9 (C^4), 204.9 (C^5), 67.5 (C^6), 72.1 (CH_2Ph), 137.5 :128.2 :127.6 :127.2 (C_6H_5), 13.3 (CH_3 at C^4), 12.6 (CH_3 at C^2).

Methyl 2-Desoxy-2,4-di-C-methyl-3-O-benzyl-6-O-mesyl-α-D-galactopyranoside (VIII). To a solution of 0.59 g (2 mmole) of (VIII) in 9 ml of CH_2Cl_2 was added 0.61 g (6 mmole) of triethylamine, the mixture cooled to −10°C, and mesyl chloride (0.47 g, 4.4 mmole) in 2 ml of CH_2Cl_2 was added dropwise, stirred for 15 min at

−10°C, diluted with 10 ml of chloroform, washed with water 1 N HCl, and $NaHCO_3$ solution, dried, evaporated, and the residue chromatographed. Yield, 0.725 g (97%), syrup, $[\alpha]_D^{21}$ +89.4° (c, 1.0).

Methyl 2,6-Didesoxy-2,4-di-C-methyl-3-O-benzyl-α-D-galactopyranoside (IX). To a solution of 0.27 g (0.72 mmole) of (VIII), in 5 ml of dry ether was added in an atmosphere of argon 0.1 g of $LiAlH_4$. The mixture was boiled for 1 h, cooled, decomposed with moist ether, and filtered, Evaporation of the filtrate gave 0.2 g (theoretical) yield of a syrup, $[\alpha]_D^{21}$ +100.7° (c, 1.0). PMR spectrum (δ, ppm): 4.44 d (1H, $J_{1,2}$ = 5 Hz, H^1), 2.1 m (1H, H^2), 3.2 m (1H, H^3), 3.64 q (1H, J_{5,CH_3} = 6 Hz, H^5), 4.58 s (2H, CH_2Ph), 7.3 s (5H, C_6H_5), 3.25 s (3H, OCH_3), 1.09 s (3H, CH_3 at C^4), 1.15; 0.96 d.d (6H, CH_3 at C^5 and C^2).

Methyl 2,6-Didesoxy-2,4,6-trimethyl-3-O-benzyl-[α]-D-galactopyranoside (X). To a solution of Me_2CuI, obtained from 3.98 g (20.9 mmole) of CuI in 25 ml of dry ether and 24.8 ml of 1.76 N Me (41.8 mmole) was added 1.95 g (5.22 mmole) of (VIII), in 15 ml of THF at −5°C. The mixture was stirred for 4 h at 10°C, decomposed with a saturated solution of NH_4Cl, washed with water, evaporated, and the residue chromatographed. Yield 1.38 g (90%), mp 81-82°C (ether−pentane), $[\alpha]_D^{21}$ +135.5° (c, 1.0). PMR spectrum (δ, ppm): 4.56 d (1H, $J_{1,2}$ = 4 Hz, H^1), 2.2 m (1H, H^2), 3.34 m (5H, H^3,H^5, OCH_3), 1.68 m (2H, H^6, $H^{6'}$), 4.08 s (2H, CH_2Ph), 7.3 s (5H, C_6H_5), 1.20; 1.06; 1.06; 1.02 m (9H, CH_3 at C^2, C^4, and C^7). ^{13}C NMR spectrum (δ, ppm): 101.9 (C^1), 37.1 (C^2), 85.3 (C^3), 72.6 (C^4), 76.4 (C^5), 22.0; 20.9 (C^6, CH_3 at C^4); 13.2 (CH_3 at C^2), 11.0 (C^7), 74.7 (CH_2Ph), 138.2, 128.4, 127.9 (C_6H_5). Found: C 69.17; H 8.65%. $C_{17}H_{26}O_4$. Calculated: C 69.38; H 8.84%.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-acetyl-β-D-galactopyranose (XIII). A mixture of 3.12 g (11.8 mmole) of (V), 15 ml of dry pyridine, 10 ml of Ac_2O, and 0.29 g (2.36 mmole) of 4-dimethylaminopyridine was kept at 20°C for 48 h. The excess of Ac_2O was decomposed with methanol, the mixture evaporated, and the residue chromatographed to give 3.10 g (86%), mp 59-60°C (ether−pentane), $[\alpha]_D^{23}$ −55.6° (c, 1.0). PMR spectrum (δ, ppm): 5.23 s (1H, H^1), 2.18 qu, (1H, J_{2,CH_3} = 8 Hz, H^2), 3.80 s (1H, H^3), 4.05 d.d (1H, H^5), 3.62 d.d (1H, $H^{6\,exo}$), 4.47 m (3H, $H^{6\,endo}$, CH_2Ph), 7.3 s (5H, C_6H_5), 1.83 s (3H, $COCH_3$), 1.74 s (3H, CH_3 at C^4), 1.07 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.7 (C^1), 38.5 (C^2), 82.0 (C^3), 77.6 (C^4), 77.3 (C^5), 64.4 (C^6), 72.2 (CH_2Ph), 138.8; 128.3, 127.7; 127.5 (C_6H_5), 170.1 ($COCH_3$), 21.7 ($COCH_3$), 23.8 (CH_3 at C^4), 16.3 (CH_3 at C^2). Found: C 66.37; H 7.02%. $C_{17}H_{22}O_5$. Calculated: C 66.6; H 7.19%.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-mesyl-β-D-galactopyranose (XIV). To 5.0 g (18.8 mmole) of (V) in 20 ml of Py was added 4.33 g (37.8 mmole) of MsCl, 20°C, 100 h, 200 ml of water, extracted with chloroform, the extract washed with 1 N HCl, a saturated solution of $NaHCO_3$, and NaCl, water, dried, evaporated, and the residue chromatographed. Yield, 3.45 g (50.3%), mp 63-63.5°C (ether) $[\alpha]_D^{23}$ −55.0° (c, 1.0). PMR spectrum (δ, ppm): 5.27 s (1H, H^1), 2.3 qu (1H, J_{2,CH_3} = 8 Hz, H^2), 3.70 m (2H, H^3, $H^{6\,exo}$), 4.18 d (1H, $J_{5,6\,exo}$ = 6 Hz, H^5), 4.51 m (3H, $H^{6\,endo}$, CH_2Ph), 7.3 s (5H, C_6H_5), 2.74 s (3H, CH_3SO_2, 1.90 s (3H, CH_3 at C^4), 1.06 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.6 (C^1), 38.8 (C^2), 82.6 (C^3), 85.7 (C^4), 77.1 (C^5), 64.4 (C^6), 71.8 (CH_2Ph), 138.3 : 128.5 :127.6 (C_6H_5), 40.1 (CH_3SO_2), 25.5 (CH_3 at C^4), 16.1 (CH_3 at C^2). Found: C 55.82; H 6.15%. $C_{16}H_{22}O_6$. Calculated: C 56.13; H 6.43%.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-mesyl-β-D-glucopyranose (XV) and 1,6-Anhydro-2-desoxy-2-methyl-3-O-benzyl-4-methylene-β-D-xylohexapyranose (XVI). A solution of 1.013 g (2.96 mmole) of (XIV) in 10 ml of $MeNO_2$ was boiled with 2 g of powdered molecular sieve 4A for 19 h, then filtered, the molecular sieve washed with ether, evaporated, and the residue chromatographed. Yield of (XV), 0.59 g (59%), mp 63.5-64°C (ehter−pentane), $[\alpha]_D^{23}$ + 4.6° (c, 8.4). PMR spectrum (δ, ppm): 4.8 s (1H, H^1), 2.42 m (1H, H^2), 3.45 d (1H, $J_{2,3}$ = 3.5 Hz, H^3), 4.7-4.0 ABX system (3H, H^5, $H^{6\,endo}$, $H^{6\,exo}$), 4.57 s (2H, CH_2Ph), 7.30 s (5H, C_6H_5), 2.86 s (3H, CH_3SO_2), 1.50 s (3H, CH_3 at C^4), 1.17 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2). ^{13}C NMR (δ, ppm): 104.7 (C^1), 38.3 (C^2), 91.9 (C^3), 82.1 (C^4), 75.4 (C^5), 62.1 (C^6), 72.9 (CH_2Ph), 137.9, 128.5, 127.7, 127.1 (C_6H_5). 44.9 (CH_3SO_2), 22.6 (CH_3 at C^4), 19.2 (CH_3 at C^4). Found: C 56.34; H 6.25%, $C_{16}H_{22}O_6S$. Calculated: C 56.13; H 6.43%. Yield of (XVI) 0.21 g (29%), syrup, $[\alpha]_D^{21}$ −4.90° (c, 1.0).

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-β-D-glucopyranose (XVII). A solution of 3.95 g (11.6 mmole) of (XV) in 25 ml of dry ether was boiled with 1 g (26 mmole) of $LiAlH_4$ until (XV) was no longer present (~30 h). Excess $LiAlH_4$ was decomposed with water (2 ml), filtered, evaporated, and the residue chromatographed. Yield 3.0 g (98.5%), syrup, $[\alpha]D^{25}$ −4.7° (c, 1.35). PMR spectrum (δ, ppm): 4.82 s (1H, H^1), 2.47 m (1H, H^2), 4.1-3.0 m (4H, H^5, $H^{6\,endo}$, $H^{6\,exo}$, OH), 4.55 q (2H, CH_2Ph), 7.30 s (5H, C_6H_5, 1.13 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2), 1.47 s (3H, CH_3 at C^4). ^{13}C NMR spectrum (δ, ppm): 104.8 (C^1), 43.7 (C^2), 93.5 (C^3), 81.8 (C^4), 73.6 (C^5), 65.5 (C^6), 70.6 (CH_2Ph), 136.9, 128.8, 128.4, 127.8 (C_6H_5), 21.7 (CH_3 at C^4), 19.6 (CH_3 at C^2).

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-β-D-glucopyranose (XVIII). A solution of 1.02 g (3.86 mmole) of (XVII) in 3 ml of DMF was treated with an excess of NaH (100 mg), stirred for 1 h, 0.5 ml

of $PhCH_2Br$ added, stirred for 2 h, 2 ml of MeOH added, poured into water (10 ml), extracted with chloroform, evaporated, and chromatographed. Yield, 1.36 g (99.5%), syrup, $[\alpha]_D^{21}$ +22.9° (c, 1.44). ^{13}C NMR spectrum (δ, ppm): 104.4 (C^1), 45.5 (C^2), 92.6 (C^3), 83.4 (C^4), 78.0 (C^5), 62.8 (C^6), 72.7 and 73.3 (CH_2Ph at C^3, C^4), 138.5 : 127.8 : 127.4 (C_6H_5), 23.3 (CH_3 at C^4), 19.4 (CH_3 at C^2).

Methyl 2-Desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-α,β-D-glucopyranoside (XX). A solution of 1.23 g (3.47 mmole) of (XVIII) in 10 g of a 5% solution of HCl in MeOH was kept at −5°C for 10 h, diluted with 100 ml of dry ether, neutralized with cooling with gaseous NH_3, NH_4Cl filtered off, evaporated, and chromatographed. Yield, 0.57 g (42.5%) of a mixture of α- and β-methylglucosides (XX), and 0.58 g (43%) of (XVIII).

Methyl 2-Desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-6-oxo-α-D-glucopyranoside (XXI). The mixture (XX) (0.101 g; 0.262 mmole) was oxidized in CH_2Cl_2 with the system $(COCl)_2$−DMSO [21]. Chromatographic separation gave 0.0483 g (48.8%) of (XXI), syrup, $[\alpha]_D^{22}$ + 166.5° (c, 0.92). PMR spectrum (δ, ppm): 4.78 d (1H, $J_{1,2}$ = 4.5 Hz, H^1), 2.5 m (1H, H^2), 3.70 d (1H, $J_{2,3}$ = 9.5 Hz, H^3), 3.64 d (1H, $J_{5,6}$ = 2.5 Hz, H^5), 8.77 d (1H, H^6), 4.0 s (2H, CH_2Ph at C^3), 4.65 qu (2H, CH_2Ph at C^4), 7.3 s (5H, C_6H_5), 3.29 s (3H, OCH_3), 1.38 s (CH_3 at C^4), 1.0 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2).

Methyl 2-Desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-6-methylene-α-D-glucopyranoside (XXII). To a suspension of the phosphorane obtained from 0.153 g (0.428 mmole) of triphenylphosphonium bromide and 0.35 ml of 1.12 N BuLi in 2 ml of benzene was added at the boil a solution of 0.483 g (0.126 mmole) of (XXI) in 1 ml of benzene, boiled for 10 min, cooled, 1 ml of acetone added, filtered, evaporated, and the residue chromatographed. Yield, 0.326 g (68%), syrup, $[\alpha]_D^{20}$ +138° (c, 0.51). PMR spectrum (δ, ppm): 4.71 d (1H, $J_{1,2}$ = 5 Hz, H^1), 2.64 m (1H, H^2), 3.72 d (1H, $J_{2,3}$ = 10 Hz, H^3), 3.70 d (1H, $J_{5,6}$ = 8.5 Hz, H^5), 6.46-5.82 m (1H, H^6), 5.36-4.90 m (2H, $=CH_2$), 4.60 q, 4.40 q (4H, CH_2Ph at C^3 and C^4), 7.30 s (5H, C_6H_5), 3.30 s (3H, OCH_3), 1.24 s (3H, CH_3 at C^4), 1.01 d (3H, J_{2,CH_3} = 7 Hz, CH_3 at C^2).

Methyl 2,6-Didesoxy-2,4,6-tri-C-methyl-3,4-di-O-benzyl-α-D-glucopyranoside (XXIII). To a solution of 0.102 g (0.267 mmole) of (XXII) and 33.3 mg of $CoCl_2$ (anhydrous) in 2 ml of THF was added with cooling at −70°C with stirring 0.12 ml of a 4.73 N solution of $LiAlH_4$ in THF, stirred for 10 min at −70°C, and the solution slowly warmed (~ 2 h) to 0°C. The mixture was decomposed with water, filtered, evaporated, and the residue chromatographed. Yield, 0.092 g (90%), syrup, $[\alpha]_D^{22}$ + 107° (c, 0.89).

1,4-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-β-D-glucopyranose (XIX). A solution of 2.86 g (18.3 mmole) of (XVII) in 20 ml of a 20% solution of HCl in MeOH was kept at 0° for 24 h, then diluted with 50 ml of dry ether, neutralized with cooling with dry NH_3, precipitated NH_4Cl filtered off, washed with ether, the filtrate evaporated, and the residue chromatographed. Yield, 2.09 g (94%), mp 83-85°C (ether−pentane), $[\alpha]_D^{21}$ +108.0° (c, 1.08). PMR spectrum (δ, ppm): 5.16 d (1H, $J_{1,2}$ = 1.5 Hz, H^1), 1.71 m (1H, J_{2,CH_3} = 7 Hz, H^2), 3.3 d (1H, $J_{2,3}$ = 10 Hz, H^3), 4.02 d (1H, $J_{5,6\ exo}$ = 5.5 Hz, H^5), 3.62 d.d (1H, $J_{6,6'}$ = 10 Hz, $H^{6\ exo}$), 4.08 d.d (1H, $J_{5,6\ endo}$ = 1 Hz, $H^{6\ endo}$), 4.73 qu (2H, CH_2Ph), 7.35 m (5H, C_6H_5), 1.38 s (3H, CH_3 at C^4), 1.05 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.4 (C^1), 42.6 (C^2), 84.1 (C^3), 73,5 (C^4), 80.6 (C^5), 64.7 (C^6), 75.0 (CH_2Ph), 138.8: 128.6 : 127.9 (C_6H_4), 21.4 (CH_3 at C^4), 13.4 (CH_3 at C^2). Found: C 67.93; H 7.27%. $C_{15}H_{20}O_4$. Calculated: C 68.18; H 7.50%.

CONCLUSIONS

The synthesis of the C^9−C^{13} fragment of erythromycin A has been accomplished, starting from levoglusan (18 steps, 3.4%).

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